

Shades of Déjerine—Forging a Causal Link between the Visual Word Form Area and Reading

In 1892, the French neurologist Jules Déjerine suggested that pure alexia resulted from an occipital lesion that selectively disconnected visual input from a region of the brain that housed “optical images of words.” In this issue of *Neuron*, Gaillard and colleagues offer evidence consistent with Déjerine’s proposal and provide new insights to the functional role of the “visual word form area.”

One of the most hotly debated topics in cognitive neuroscience is whether visual object recognition is best understood within the context of a general or modular architecture. Functional brain imaging studies have provided considerable evidence for a modular view. These studies have identified partially distinct neurocircuits for representing different properties of an object such as what it looks like, how it moves, and how it is manipulated (Martin and Chao, 2001). Prominently included in these networks are patches of ventral occipitotemporal cortex presumed to represent features of visual form associated with certain object categories such as faces, tools, and places. Moreover, the general topological layout of these regions is relatively uniform from one person to another, suggesting the possibility of a highly constrained, and perhaps genetically determined, organization by object category. Of all the claims for a category-specific brain region, perhaps the most controversial has been the visual word form area (VWFA), purportedly located in the left occipitotemporal sulcus bordering the fusiform gyrus (McCandliss et al., 2003). How could there be a piece of neural tissue dedicated to a recently invented cognitive skill like word recognition? Gaillard and colleagues (2006) report a unique set of findings in favor of the existence of the VWFA that will surely add fuel to the debate.

The data were obtained from a patient who developed a reading disorder referred to as “pure alexia.” In this disorder, the previously simple, automatic skill of reading can be accomplished only in a laborious letter-by-letter manner. Visual object recognition remains intact, as do other language skills including the ability to write—hence the disorder is also called “alexia without agraphia.” This term was coined by Déjerine, who first reported the disorder in 1892. To account for the impairment, Déjerine suggested that his patient had suffered a lesion of the left occipital lobe—supported by the presence of a dense right homonymous hemianopia—that also impinged on fibers carrying visual information from the intact right hemisphere. As a result, the flow of visual information was selectively disrupted to a region in the left hemisphere that housed “optical images of words” (Déjerine, 1892). Since Déjerine’s initial report, the association between pure alexia and a left occipital lesion has been repeatedly confirmed (e.g., Binder and

Mohr [1992]). More recently, functional brain imaging studies by fMRI (Polk and Farah, 1998; Cohen et al., 2000) and electrophysiological recordings directly from the cortical surface of the human temporal lobe (Nobre et al., 1994) have provided additional evidence for the VWFA.

Of course, these claims have not gone unchallenged (Price and Devlin, 2003, 2004). Questions have been raised as to whether a ventral occipitotemporal lesion is necessary and sufficient to cause pure alexia and whether the reading disorder is categorical (limited to letters and or words) or a manifestation of a more general visual processing deficit (Price and Devlin, 2003). Careful examination of a patient may uncover visual recognition deficits for other object categories that could reflect an impairment of a mode of processing common to words and other object types. Data on a patient’s premorbid level of cognitive functioning are rarely available, raising questions about the extent of change that can be directly ascribed to the lesion. Indeed, arguments about whether “category-specific” disorders are best explained by a modular or general processing architectures have long dominated the history of thinking about the agnosias (e.g., Bay [1953]).

The neuroimaging data also have been challenged. Some investigators have failed to find a region in occipitotemporal cortex more responsive to visually presented words than other objects. In addition, the purported location of the VWFA has been shown to be active during many nonreading tasks, thus questioning claims for specificity (Price and Devlin, 2003, 2004). Finally, even when neuroimaging has provided supportive evidence, those findings are silent about whether the VWFA has a causal role in reading. The data provided by Gaillard and colleagues directly address these caveats and concerns.

The evidence consists of pre- and postoperative cognitive and fMRI testing, as well as electrophysiological recordings of local field potentials (LFPs) obtained prior to surgical intervention for intractable epilepsy. Prior to surgery, the patient performed normally on a battery of neuropsychological measures. Importantly, object naming, face recognition, and language skills, including single-word reading and writing to dictation, were intact. Moreover, time to read single words did not vary with word length. As typically found in normal readers, there was no appreciable increase in reading time for common words that varied in length from three to eight letters.

Word and object recognition were further evaluated by fMRI. Largely consistent with previous findings with healthy individuals (Martin and Chao, 2001; Yovel and Kanwisher, 2004), the patient’s activation map revealed discrete regions in ventral and lateral occipitotemporal cortex associated with identifying faces, tools, and houses. In addition, a region of activity centered on the left occipitotemporal sulcus and including the fusiform gyrus, responded more to words than the other object categories, consistent with previous reports of the location of the VWFA. Thus, prior to surgery, the patient’s

visual recognition performance and pattern of neural activity in posterior cortex for words and objects was normal. Moreover, LFPs recorded from the implanted electrodes closest to the VWFA showed that this region was sensitive to lexical frequency, but not word length, again consistent with the functional characteristics of the VWFA.

The epileptic focus was localized to the left occipital lobe based on recordings from the implanted electrodes. Surgery was successful in eliminating the patient's seizure disorder. Object naming and face recognition ability were unchanged, with performance remaining essentially at ceiling on standard clinical measures. Language skills, including writing to dictation, remained normal as well. However, the patient complained of reading difficulty, and this complaint was subsequently documented by a re-evaluation of single-word reading 6 months after surgery. In contrast to presurgical performance, reading was now markedly slowed and inaccurate. Moreover, reading times increased linearly with increases in word length. Thus, whereas prior to surgery it took the patient ~600 ms to read a word, regardless of word length, after surgery, reading was slowed to ~1000 ms for three-letter words and increased by ~100 ms per additional letter (i.e., letter-by-letter reading).

Given this unfortunate behavioral consequence, the critical question now was: what changes, if any, occurred to the patterns of neural activity associated with word and object recognition? The site of the cortical excision was just posterior to the location of the VWFA identified during the preoperative fMRI evaluation, as well as by presurgical cortical recordings. Post-surgical fMRI evaluation replicated the previous findings for viewing concrete objects. Category-related neural activity was observed for viewing faces, houses, and tools and the locations of these activations remained essentially unchanged. However, words now failed to elicit any activity in the patient's previously identified VWFA. Not only was the VWFA no longer more responsive to words than the other objects, this region of cortex failed to respond even when words were contrasted with viewing a simple visual fixation point. To account for this striking finding, the authors suggested that as a result of the surgical excision, the VWFA was deprived of its normal input and thus was no longer able to perform its dedicated function of automatically identifying visually presented letters. Thus, the patient's pure alexia arose from a disconnection lesion, just as Déjerine suggested well over 100 years ago.

But if the VWFA was no longer functioning, how do we account for the patient's remaining letter-by-letter reading? Clues to answer this question were provided by another fMRI investigation that evaluated covert reading of consonant strings and real words. In contrast to the fMRI study with objects, the alphabetic material was presented for a considerably longer duration and at a slower rate to allow for letter-by-letter reading. Activity was observed in regions of the occipital lobe, bilaterally, as well as in a region close to the previously identified VWFA area. However, whereas presurgically the VWFA region responded to consonant strings and real words—a defining feature of the VWFA—the postsurgical VWFA activation was wholly limited to reading real

words. Moreover, relative to preoperative scanning, the postsurgical imaging data revealed heightened activity in a widely distributed network that included left frontal, parietal, and temporal sites. Based on these findings, the authors suggest that letter-by-letter reading was accomplished via top-down input to intact regions of posterior occipitotemporal cortex from frontal and parietal regions that were also active during covert reading postsurgically. Indeed, previous studies have linked these frontal and parietal regions to visual scanning (frontal eye fields), lexical search (lateral prefrontal cortex), attentional processes (posterior parietal cortex), and effortful cognition (anterior cingulate).

Of course, many questions remain to be answered. Is there a single VWFA or a collection of closely aligned regions, each performing a different role in word reading? For example, is there a distinct cortical region for letter processing, another for pronounceable letter strings, and another for combining orthographic and phonological information (i.e., a multimodal word form area) (Cohen et al., 2004)? How visual word representations link up with lexical and conceptual representations also remains to be determined.

Also left unresolved is the vexing problem of how to account for the intersubject consistency in the general location of the VWFA and other category-related regions in ventral occipitotemporal cortex. One possibility is that the VWFA performs a visual processing function that predisposed it to being co-opted for reading. The origin of this processing bias, in turn, may be related to bottom-up features of the visual processing system (e.g., retinotopic organization) (Malach et al., 2002) and/or physical features of the stimuli themselves (e.g., spatial frequency). Top-down influences may also play a prominent role in the form of predetermined connections between regions of occipitotemporal cortex and other brain areas. For example, the VWFA may have developed its role in reading because of, in part, privileged access to information originating in frontal and temporal regions that support language. Indeed, the possibility that different regions of ventral occipitotemporal cortex receive privileged bottom-up and top-down inputs may provide important clues to understanding the organization of object category-related information in this region of the brain.

The single case study described by Gaillard and colleagues provides compelling evidence that the VWFA plays a causal role in the chain of neural events that underlie normal reading. Although questions may be raised about the limitations of each of the experiments performed, the total impact is greater than the sum of the parts. Their achievement is all the more impressive given the difficulties inherent in obtaining behavioral, neuroimaging, and electrophysiological data in a clinical setting. Efforts should now be directed toward understanding the specific online processing computations and storage characteristics of the VWFA and other category-related regions that allow for both a modular architecture and the remarkable flexibility of human cognition.

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Nob Mice Wave Goodbye to Eye-Specific Segregation

Spontaneous retinal activity is necessary to establish and maintain eye-specific projections to the LGN, but whether the spatial and temporal structure of this activity is important remains unclear. A new study by Demas et al. in the current issue of *Neuron* shows that when the frequency of spontaneous retinal waves is increased and waves abnormally persist past eye opening, eye-specific projections to the LGN desegregate. These results provide important new insight into the mechanisms that drive eye-specific refinement and stabilization.

The electrical activity of a developing neuron has a profound effect on the number and location of synapses it can form, but it is unclear how the pattern and timing of this activity are important. Eye-specific visual connections are a well-established model system for investigating how activity sculpts precise circuitry. In mammals, eye-specific retinogeniculate projections emerge from an initially imprecise state in which retinal ganglion cell (RGC) axons from the two eyes intermingle in the lateral geniculate nucleus (LGN), but subsequently segregate into eye-specific domains. This segregation occurs before the onset of sensory experience at a time when spontaneous “waves” propagate across the retina, inducing neighboring RGCs to fire synchronously. The temporal and spatial structure of retinal waves ensures that nearby RGCs are correlated in their firing and that RGCs located far apart or in different eyes do not fire together (Wong, 1999). Spontaneous retinal activity is necessary for both the segregation and maintenance of eye-

specific inputs to the LGN (Penn et al., 1998; Chapman, 2000) and acts by driving a competitive axon-pruning process for synaptic target territory. If activity is eliminated or increased only in one eye, segregation still occurs, but the more active eye acquires more synaptic territory in the LGN at the expense of the less active eye (Penn et al., 1998; Stellwagen and Shatz, 2002).

Do the spatial and temporal features of retinal wave activity instruct eye-specific segregation or does activity simply play a permissive role? When the correlated firing of neighboring RGCs is diminished, as occurs in mice that lack the $\beta 2$ subunit of the nicotinic acetylcholine receptor ($\beta 2$ nAChR^{-/-}), retinotopic maps fail to refine in the LGN, superior colliculus, and visual cortex (McLaughlin et al., 2003; Grubb et al., 2003; Cang et al., 2005). $\beta 2$ nAChR^{-/-} mice also exhibit defects in eye-specific retinogeniculate segregation (Rossi et al., 2001), which has been attributed to a loss of high-frequency RGC bursting during wave activity (Torborg et al., 2005). Approximately 40% of RGCs, however, are silent in $\beta 2$ nAChR^{-/-} mice, whereas the rest of the RGCs exhibit significantly elevated spiking (McLaughlin et al., 2003). It is thus unclear whether the retinotopic and eye-specific defects observed in $\beta 2$ nAChR^{-/-} mice are due only to a loss of correlated RGC firing. The significantly elevated activity in some of the RGCs, for instance, might have enhanced their axon outgrowth and branching (Goldberg et al., 2002). Indeed, other studies report that if correlated RGC firing is disrupted but activity levels are kept stable, eye-specific retinogeniculate segregation occurs normally (Huberman et al., 2003). Those findings, combined with evidence that eye-specific layers can develop in the absence of binocular interactions (Williams et al., 1994), led to the hypothesis that axon guidance cues mediate eye-specific targeting in the LGN. However, in these experiments, some unknown (but nonetheless essential) features of spontaneous activity may have remained intact within the retina, thereby allowing eye-specific segregation to proceed. Recent findings demonstrate that axon guidance cues do indeed influence eye-specific pathfinding in the LGN (Huberman et al., 2005; Pfieffenberger et al., 2005), but rather than ruling out a role for activity, these results suggest a two-step model in which guidance cues mediate the initial targeting of retinogeniculate axons and then activity enhances their segregation. However, the features of activity that drive eye-specific segregation remain unclear.

The results of Demas et al. (2006) provide exciting new evidence that the pattern and timing of retinal waves actively maintain eye-specific retinogeniculate segregation. They examined no b-wave (*nob*) mutant mice that lack the b-wave component of the retinal ERG. The b-wave normally results from rod photoreceptor to ON-bipolar cell transmission. Demas et al. (2006) compared the spatiotemporal patterns of spontaneous RGC spiking in *nob* and wild-type (wt) mice by using multisite electrode array recordings in vitro and by recording directly from the optic nerves in vivo. During the stage when eye-specific segregation occurs from birth until postnatal day 12 (P12), spontaneous retinal activity is normal in *nob* mice. Mice open their eyes around P15, and waves normally disappear shortly after that time. However, beginning at P15, and continuing